



Antiviral Agents, Topical

Therapeutic Class Review (TCR)

November 21, 2011

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
acyclovir cream (Zovirax®) ¹	Valeant	Treatment of recurrent herpes labialis (cold sores) in adults and children 12 years of age and older
acyclovir ointment (Zovirax®) ²	Valeant	Management of initial genital herpes and in limited non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients
acyclovir/hydrocortisone (Xerese™) ³	Valeant	Early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in adults and children 12 years of age and older
docosanol (Abreva®) ⁴	GSK	Treatment of cold sores/fever blisters on the face or lips in adults and children 12 years of age and older to shorten healing time and duration of symptoms
penciclovir (Denavir) ⁵	New American Therapeutics	Treatment of recurrent herpes labialis (cold sores) in adults and children 12 years of age and older

OVERVIEW

Herpes labialis is an infection of the lips or "perioral" (around the mouth) area. The primary infection is usually asymptomatic; however, it can also present itself as herpes simplex virus (HSV) gingivostomatitis (of the mouth and gums). Herpes labialis (fever blisters, cold sores) can be caused by either herpes simplex virus-1 (HSV-1) or herpes simplex virus-2 (HSV-2). While the primary (first episode) infections with HSV-1 or HSV-2 do occur, recurrences are generally the result of HSV-1 infection. Oral recurrences with HSV-2 are very rare.

About 80 percent of the general adult population has serologic infection with HSV-1 with only about 30 percent of these individuals having clinically significant outbreaks. In the United States, approximately 130 million individuals over the age of 12 years are infected with HSV-1.^{6,7,8} Approximately 20 percent of the adult population in the United States is seropositive for HSV-2.

Most people acquire HSV-1 asymptotically. Once a person begins to produce antibodies, the infection becomes latent in the sensory ganglia. HSV-1 infection remains latent in the trigeminal ganglia and HSV-2 in the sacral ganglia. The viruses become reactivated secondary to certain stimuli including fever, physical or emotional stress, ultraviolet light exposure, and axonal injury. Most recurrent episodes of herpes labialis are preceded by a prodromic phase which may consist of tingling, itching, or redness. These can last for up to 24 hours before lesion development. Recurrent infections tend to be less severe because of existing cellular and humoral immunity from prior exposures. Infection by HSV requires a break in the skin's barrier; intact skin is resistant to the virus.

Recurrent herpes labialis exists in a subset of patients infected with herpes labialis. Most patients with recurrent herpes labialis have less than two occurrences per year.⁹ The rate of recurrence of genital herpes depends on a number of factors including viral type, prior immunity to autologous or heterologous virus, gender, and immune status of the host.¹⁰

Antiviral therapy includes both oral and topical preparations. Oral treatments have long been the standard of care for most patients, as supported by clinical trials.^{11,12,13,14} Oral antivirals are commonly used as preventative care as well. Patients will take a low-dose oral antiviral daily to help prevent an

outbreak or initiate treatment when they feel an episode coming on to help prevent a lesion. Suppressive therapy should be considered in patients with recurrent herpes labialis which manifest six or more times per year.¹⁵ The topical preparations are reserved for treatment of an active lesion. Topical preparations should be started as early as possible in the prodrome phase in order for treatment to be most beneficial.

Topical acyclovir was touted as effective in preventing herpes simplex labialis in 1983, but further trials cast doubt about whether it can significantly alter the course of disease and normal healing.^{16,17} Suppression studies produced promising results, notably clinical trials that demonstrated significant differences favoring acyclovir in terms of healing time.^{18,19} Topical penciclovir later demonstrated that it had similar antiviral properties as acyclovir. Although comparison trials have not been performed, studies showed penciclovir was as efficient in reducing healing time as other topical preparations on the market.²⁰

Docosanol (Abreva) is the only FDA-approved OTC medication to treat cold sores/fever blisters. It reduces healing time and duration of symptoms of herpes labialis.

PHARMACOLOGY^{21,22,23,24,25}

Acyclovir is a synthetic purine nucleoside analogue with inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). This inhibitory activity is highly selective due to its affinity for the enzyme thymidine kinase (TK). This enzyme converts acyclovir into acyclovir monophosphate, a nucleoside analogue which is further converted into diphosphate and then into triphosphate. Acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in three ways: first, by competitive inhibition of viral DNA polymerase; second, incorporation into and termination of growing viral DNA chains; and third, inactivation of viral DNA polymerase. This phosphorylation is done more efficiently by HSV; therefore, a greater antiviral activity against HSV exists.

Penciclovir has a similar mechanism of action as acyclovir. It is highly selective for HSV-1 and HSV-2 infected cells which may be attributed to two factors. First, viral thymidine kinase phosphorylates penciclovir more rapidly than cellular thymidine kinase. Therefore, the active penciclovir triphosphate is present at a higher concentration in HSV-infected cells than in uninfected cells. Second, the activated drug binds to viral DNA polymerases with a higher affinity than to human DNA polymerases. As a result, penciclovir exhibits negligible cytotoxicity to healthy cells. Penciclovir appears at least as effective as acyclovir as an inhibitor of herpes virus DNA synthesis.

The exact mechanism of action of docosanol is not known. Docosanol is not directly virucidal but is indirectly involved with viral replication. This inhibition is due to the ability of docosanol to block the fusion of lipid-enveloped viruses (e.g. HSV-1 and HSV-2) with cell membranes. This in turn leads to inhibiting cellular entry, nuclear localization, and subsequent viral replication. The development of resistance to docosanol is unlikely since it modulates the host cell to prevent viral entry and does not inhibit the synthesis or replication of the virus.

Hydrocortisone is the primary glucocorticoid secreted by the adrenal cortex. Hydrocortisone can be applied topically in order to suppress the clinical signs of diseases, such as herpes labialis, where inflammation is a prominent feature.

PHARMACOKINETICS

Systemic absorption of all the topical antiviral agents is low.^{26,27,28} However, the therapeutic effects of antiviral drugs in treating herpes labialis are evident when the cellular concentration of the drug approaches an optimum level. Oral acyclovir (even in high doses) does not produce the concentration necessary to generate that level of response consistently, despite positive results. Penetration of topical preparations of acyclovir through the stratum corneum has proven difficult.^{29,30} The cream formulation has exhibited greater penetration in herpes labialis compared to the ointment formulation, however comparative studies have not been performed to compare their efficacy.^{31,32} In contrast to acyclovir, penciclovir has a prolonged half-life (10 – 20 times longer) in HSV-infected cells.³³

Topical corticosteroids can be absorbed through intact skin and have systemic side effects. Applying topical corticosteroids to abraded or inflamed skin may increase systemic absorption and side effects.³⁴ Once absorbed through skin, topical corticosteroids act similar to systemically administered corticosteroids and are metabolized by the liver and excreted by the kidneys. Topical corticosteroids and their metabolites can also be excreted into the bile.

CONTRAINDICATIONS/WARNINGS^{35,36,37,38,39}

Hypersensitivity to these agents and any of their components is considered a contraindication. These agents are for topical use only. They should not be used for ophthalmic, intranasal, intraoral, intravaginal use, or in or near the eyes. Discontinue if sensitization or severe local irritation occurs.

Acyclovir, penciclovir, and docosanol cream should only be used on herpes labialis on the lips and face. Because no data are available, it is not recommended to apply acyclovir or penciclovir cream to mucous membranes. The effects of acyclovir, penciclovir, and docosanol cream have not been established in immunocompromised patients.

There are no data to support the use of acyclovir ointment 5% to prevent transmission of infection to other persons or prevent recurrent infection when applied in the absence of signs and symptoms. It should not be used to prevent recurrence of HSV infection.

DRUG INTERACTIONS^{40,41,42,43,44}

Clinical experience has identified no interactions resulting from systemic or topical administration of other drugs concomitantly with any of these agents. Drug interaction studies have not been performed with acyclovir/hydrocortisone (Xerese).

ADVERSE EFFECTS

Drug	Application Site Irritation	Pruritus	Rash	Headache	Pain	Allergic Reaction
acyclovir cream (Zovirax) ⁴⁵	5	<1	<1	nr	<1	<1
acyclovir ointment (Zovirax) ⁴⁶	nr	4	nr	nr	30	nr
acyclovir/hydrocortisone (Xerese) ⁴⁷	<1	nr	nr	nr	nr	reported
docosanol (Abreva) ^{48,49}	2.9	0.4	0.5	10.4	reported	nr
penciclovir (Denavir) ^{50,51}	1.3	0	0.1	5	0	0

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

SPECIAL POPULATIONS^{52,53,54,55,56,57}

Pediatrics

An open-label, uncontrolled trial with acyclovir (Zovirax) 5% cream was conducted in 113 patients aged 12 to 17 years with herpes labialis. In the study, therapy was applied using the same dosing regimen as in adults, and subjects were followed for adverse events. The safety profile was similar to that observed in adults. Acyclovir (Zovirax) cream is indicated for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older).

Safety and effectiveness of acyclovir (Zovirax) 5% ointment in pediatrics have not been established.

Safety and efficacy of penciclovir (Denavir) 1% cream in children less than 12 years of age have not been established.

Docosanol (Abreva) cream is indicated in patients 12 years of age and older. The safety and effectiveness of docosanol have not been established in children.

Acyclovir/hydrocortisone (Xerese) cream 5%/1% is indicated in patients 12 years of age and older. The safety and effectiveness of acyclovir/hydrocortisone have not been established in children.

An open-label safety study in adolescents with recurrent herpes labialis was conducted in 134 subjects. Subjects had, on average, four episodes of herpes labialis in the previous 12 months. The median age was 14 years (range 12 to 17 years); 50 percent were female and all were Caucasian. Therapy was applied using the same dosing regimen as in adults and subjects were monitored for adverse events and selected efficacy parameters. The safety and efficacy profile appeared similar to that observed in adults.⁵⁸

Pregnancy

All agents are Pregnancy Category B except for docosanol. No adequate and well-controlled studies have been performed with docosanol in pregnant women.

Dosages^{59,60,61,62,63,64}

Drug	Patients age 12 years and older	Availability
acyclovir cream (Zovirax)	Applied 5 times per day for 4 days	2 gm, 5 gm tube of 5% cream
acyclovir ointment (Zovirax)	Applied every 3 hours or 6 times per day for 7 days	30 gm tube of 5% ointment
acyclovir/ hydrocortisone (Xerese)	Applied 5 times per day for 5 days	5 gm tube of 5% acyclovir/ 1% hydrocortisone cream
penciclovir (Denavir)	Applied every 2 hours during waking hours for a period of 4 days	1.5 gm, 5 gm tube of 1% cream
docosanol (Abreva)	Applied 5 times per day until lesion is healed	2 gm tube, of 10% cream

CLINICAL TRIALS**Search Strategy**

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled trials studying agents within this class for the FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no published head to head trials comparing docosanol, acyclovir, and penciclovir in the treatment of herpes labialis. Due to the lack of studies, placebo-controlled trials have been included.

There are no current studies available for acyclovir (Zovirax) ointment. Previous placebo controlled studies have been performed and showed that acyclovir ointment was more effective at reducing healing time and, in some cases, duration of viral shedding and pain in immunocompromised patients with herpes labialis.⁶⁵

acyclovir (Zovirax) cream versus penciclovir (Denavir)

A randomized, double-blind, active comparator study enrolling 248 patients with a diagnosis of herpes simplex facialis/labialis compared penciclovir 1% cream and acyclovir 3% cream.⁶⁶ Patients were evaluated before treatment and on days three, five, and seven of treatment. No severe adverse events were recorded in either treatment group. There were no significant differences in the efficacy endpoint or cure rate between groups, but a trend towards a shorter time to resolution of all symptoms, cessation of new blisters, and loss of crust ($p \leq 0.08$) was seen with the penciclovir group. In addition,

the clinical scores in penciclovir treated patients were significantly lower than those in the acyclovir group on days five and seven ($p \leq 0.05$). The study used acyclovir cream at a lower strength than the currently available US formulation.

acyclovir/hydrocortisone cream (Xerese) versus placebo

A double-blind, randomized, placebo-controlled study was performed to compare the efficacy of 5% acyclovir/1% hydrocortisone cream for treatment of UV radiation-induced herpes labialis.⁶⁷ A total of 380 immunocompetent patients received UV radiation (UVR) in order to induce a herpes labialis recurrence. Patients were randomized to receive either 5% acyclovir/1% hydrocortisone cream ($n=190$) or placebo ($n=190$) and were instructed to apply treatment six times per day for five days, beginning on the morning of the second day after UVR exposure. "Immediate lesions," defined as those that arose within two days of UVR are of uncertain etiology and pathophysiology and were noted but not monitored. "Delayed lesions," defined as lesions that occurred two to seven days after exposure to UVR, were evaluated. Of the 380 UVR exposed patients, 120 patients developed delayed lesions and were included in the intent-to-treat population. Fifty (26 percent) of the 190 patients treated with active drug developed delayed lesions, whereas 70 (37 percent) of the 190 patients treated with placebo developed delayed lesions, which was a reduction of 29 percent ($p=0.022$). Healing time, measured as the time to normal skin, was reduced in the active treatment population compared to placebo, nine days versus 10.1 days ($p=0.04$), respectively. There was a trend in reduction in the maximum lesion size in the active treatment group by 28 percent compared to that in the controls (43 versus 60 mm², respectively; $p=0.07$). The active treatment reduced the number of patients with moderate to severe tenderness but had no effect on lesion pain. Compared to placebo, 5% acyclovir/1% hydrocortisone cream provided benefits to patients in reducing lesion incidence, healing time, lesion size, and lesion tenderness. The recommended dosage for 5% acyclovir/1% hydrocortisone cream is five times per day for five days.

In a double-blind study, 1,443 patients with recurrent labial herpes were randomized to receive acyclovir 5%/hydrocortisone 1% cream, 5% acyclovir in Xerese vehicle, or vehicle alone.⁶⁸ The subjects had, on average, 5.6 episodes of herpes labialis in the previous 12 months. Subjects were provided with directions to apply their product five times per day within one hour of noticing signs or symptoms and to continue treatment for five days. Ulcerative cold sores occurred in 58 percent of the subjects treated with combination cream compared to 65 percent in subjects treated with 5% acyclovir in Xerese vehicle and 74 percent in subjects treated with vehicle alone. The mean time for the subject's skin to return to normal was approximately 1.6 days shorter in the subjects treated with combination cream compared to vehicle. Size of the cold sore and symptoms such as tenderness were reduced with combination cream as compared to vehicle.

penciclovir (Denavir) versus placebo

Two randomized, double-blind, parallel group studies were performed with 3,057 patients of which 83 percent developed clinical lesions. Patients were given either penciclovir 1% cream or placebo for the treatment of recurrent herpes simplex labialis defined as three or more episodes a year that typically manifested as classical lesions.⁶⁹ Patients self-initiated treatment within one hour of noticing the first signs and symptoms of a recurrence and were required to apply medication six times per day for the first day and every two hours while awake for four consecutive days. The penciclovir-treated group lost

lesions 31 percent faster than the placebo-treated group ($p=0.0001$) and experienced 28 percent faster resolution of lesion pain ($p=0.0001$). Dosing frequency was vital to treatment outcomes.

docosanol (Abreva) versus placebo

Two identical multicenter, double-blind, placebo-controlled studies were performed with 737 patients who were given either docosanol 10% cream or placebo for the treatment of herpes simplex labialis in the prodrome or erythema stage.⁷⁰ Patients were treated five times daily until healing occurred (i.e., the crust fell off spontaneously or there was no longer evidence of an active lesion). The median time to healing in the docosanol-treated group ($n=370$) was 4.1 days, 18 hours shorter than that of the placebo-treated group ($n=367$) ($p=0.008$). The docosanol group also exhibited reduced times from treatment initiation to cessation of pain and all other symptoms ($p=0.002$), complete healing of lesion ($p=0.023$), and cessation of the ulcer or soft crust stage of the lesion ($p<0.001$). Aborted episodes were experienced by 40 percent of docosanol patients and 34 percent of placebo patients ($p=0.109$). Adverse events with docosanol were mild and similar to those with placebo. The study concluded that docosanol applied five times per day is safe and effective in the treatment of recurrent herpes simplex labialis.

SUMMARY

Herpes labialis is a highly prevalent disease state within the U.S. population. The HSV-1 and HSV-2 viruses become reactivated secondary to certain stimuli including fever, physical or emotional stress, ultraviolet light exposure, and axonal injury. Low dose oral antiviral medications have provided a preventative treatment option for patients with recurrent herpes labialis. Topical antiviral medications are used for the treatment of an active lesion and should be started during the prodrome phase, characterized by perioral tingling, itching, and redness, to be most beneficial. The utilization of topical antiviral treatments has increased especially since the addition of the OTC preparation, docosanol (Abreva). Left untreated, herpes labialis may take up to 10 days or more to heal.

The pharmacokinetics, contraindication/warnings, drug interactions, and adverse effects are very similar between acyclovir, penciclovir, and docosanol. Likewise, no significant difference exists when examining the products' FDA approved application frequency and duration of therapy. Overall, acyclovir, penciclovir, and docosanol for herpes labialis treatment only provides modest benefit if used very early in the prodrome phase.

Comparative literature examining topical antiviral therapies is lacking. According to studies, all products are effective in treating herpes labialis and provide symptom relief such as decreased lesion count, lesion size, pain, and healing time compared to placebo. Penciclovir (Denavir) did provide better clinical scores compared to acyclovir (Zovirax) cream in one study; however the study used a lower strength of acyclovir (Zovirax) cream than the currently available US formulation. Docosanol (Abreva) does offer an advantage to patients in that it is available without a prescription.

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